Review Article

Skin Regenerative Potentials of Curcumin

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Abstract

Curcumin, an active constituent of the spice turmeric, is well known for its chemopreventive properties and is found to be beneficial in treating various disorders including skin diseases. Curcumin protects skin by quenching free radicals and reducing inflammation through the inhibition of nuclear factor-kappa B. Curcumin also affects other signaling pathways including transforming growth factor-β and mitogen-activated protein kinase pathway. Curcumin also modulates the phase II detoxification enzymes which are crucial in detoxification reactions and for protection against oxidative stress. In the present review, the biological mechanisms of the chemopreventive potential of curcumin in various skin diseases like psoriasis, vitiligo, and melanoma is discussed. The application of curcumin in skin regeneration and wound healing is also elucidated. We also explored the recent innovations and advances involved in the development of transdermal delivery systems to enhance the bioavailability of curcumin, particularly in the skin. Recent clinical trials pertaining to the use of curumin in skin diseases establishes its benefits and also the need for additional clinical trials in other diseases are discussed. © 2013 BioFactors, 39(1):141–149, 2013

Keywords: *curcumin; skin regeneration; anticancer; wound healing; chemoprevention*

1. Introduction

Curcumin (diferuloylmethane), a major active component of the dietary spice turmeric, has been used in Indian and Chinese medicine for treatment of various disease conditions. Curcumin is a polyphenol and possesses anti-inflammatory, antioxidant, antiproliferative, and wound healing properties [1]. The disease portfolio for this traditional medicine include pain disorders, digestive diseases, menstrual difficulties, skin conditions, sprains, wounds, and liver disorders [2]. Curcumin has the potential to preserve food through its antioxidant property [3]. Laboratory studies have also confirmed that curcumin possess antioxidant, anti-inflammatory, antiviral, antibacterial, antifungal, and anticancer activities [4–6].

Recently, mechanistic studies have established that these effects are mediated through the regulation of various transcription factors, growth factors, inflammatory cytokines, protein kinases, and other enzymes [7]. Skin is a lipid rich tissue and neutralizing of free radicals, reduction of inflammation, modulation of abnormal cell growth, reduction of UV damage and the slowing of the accumulation of age related pigments in the skin is essential for skin care and treatment. Curcumin protects skin by quenching free radicals and reducing inflammation through nuclear factor-kappa B (NF-κB) inhibition [8]. Curcumin has also been shown to partially prevent UV damage as well as help to lower the incidence of tumors on the skin of mice [8]. Human studies are still needed to fully understand the benefits of curcumin related to the skin diseases and regeneration. Here, we review the recent advances and chemopreventive role of curcumin in various skin diseases.

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2. Chemopreventive Role of Curcumin in Skin Diseases

Skin is the largest organ of the body and is made up of tissue layers, which protect underlying muscles and organs. The most important role of skin is to protect our body against heat, light, infection, and injury. Skin is the first line of defense and is vulnerable to various adverse conditions, such as rashes, burns, injuries, infections, and disorders, such as scleroderma, dermatitis, psoriasis, and cancer. Skin damage is also a serious side effect of radiation therapy for tumors. Several studies showed the protective effect of curcumin against various chemicals and environmental pollutants that cause skin damage [9]. Chemoprevention is the use of a substance of chemical, natural, or synthetic origin to prevent, hamper, arrest, or reverse a disease. Curcumin has been widely studied during the past few decades as a chemopreventive agent due to its nontoxic nature. Turmeric was prescribed for the treatment of various skin disorders such as acne, skin rashes and warts in Ayurvedic and Chinese systems of medicine. Curcumin traditional use in skin conditions and its safety profile makes it an ideal candidate for chemoprevention. There is recently an increasing interest in elucidating the molecular mechanisms of curcumin in treating various skin conditions.

Psoriasis, a common chronic inflammatory disease of the skin and joints, is associated with significant decrements in health-related quality of life, multiple comorbidities, and increased cardiovascular risk and mortality [10]. Treatment options for severe psoriasis are either time-consuming or have the potential for organ toxicity with chronic use [10]. A strong scientific rationale which will be discussed in the following paragraph suggests that curcumin may in fact be a promising agent for the treatment of psoriasis. Both *in vitro* and *in vivo* studies have demonstrated the inhibitory effect of curcumin on immune pathways critical to the pathophysiology of psoriasis such as NF-κB and its downstream inflammatory gene products including Th-1-type cytokines (*i.e.*, tumor necrosis factor (TNF)-α, interferon-γ) [10]. TNF-α, a key proinflammatory cytokine, implicated in various skin diseases, such as psoriasis and atopic dermatitis [11,12], induces proinflammatory cytokines, including IL-1β, IL-2, IL-6, IL-8, a IL-10, IFN-α, and causes the activation of NF-κB and mitogen-activated protein kinase (MAPK) [13,14]. Recently, several drugs have been developed to treat psoriasis through inhibiting TNF-α [15,16]. One of the TNF-α targets is ERK, which has recently been shown to upregulate the expression of cyclin E and also results in accumulation of cyclin D1 [17]. In addition, p38 MAPK and c-Jun NH2-terminal kinase (JNK) are highly activated by TNF-α treatment in keratinocytes [18], and activation of p38, and JNK are associated with the expression of proinflammatory cytokines such as IL-6 and IL-8 [19–21]. Psoriasis is also characterized by hyperproliferation and abnormal differentiation of keratinocytes. Curcumin is a selective phosphorylase kinase inhibitor, which has been shown to have anti-inflammatory and antiproliferative properties and decrease the expression of proinflammatory cytokines in psoriatic keratinocytes [22]. In addition, Grandjean-Laquerriere et al. reported that curcumin attenuates the expression of ultraviolet B (UVB)-induced IL-6 and IL-8 in keratinocytes partially through the inhibition of NF-κB activation [23]. Curcumin is known to exert its anti-inflammatory action in various cell lines through the inhibition of NF-κB, AP-1, and MAPK pathways [24–27]. Cho et al. also showed that curcumin inhibited NF-κB and MAPK pathway to decrease cell proliferation as well as reduce the expression of IL-6 and IL-8 in TNF-α-treated keratinocytes [28]. Hence, it may be a good strategy to achieve broad anti-inflammatory effects through the inhibition of TNF-α, NF-κB, and MAPK by curcumin.

Curcumin decreased the expression of transforming growth factor-β (TGF-β) and extracellular matrix in keloid fibroblasts suggesting their utility in the treatment of keloids, a fibrotic disease of the skin characterized by skin overgrowth [29]. Scleroderma is another fibrotic disease of the skin and curcumin may exert antifibrotic effect [30] for managing scleroderma by mechanisms involving suppressing TGF-β. Vitiligo, a depigmenting disease of human skin is characterized by localized loss of melanin from the lesional epidermis [31–33]. It is well established that the restoration of the skin color can be achieved after the reduction of epidermal H_2O_2 levels [34,35]. Turmeric is widely used for wound healing and skin lightening in Asia [36] and is also known for its antioxidant, anti-inflammatory, and anticarcinogenic properties [37–39]. Vitilgo treatment by combination therapy using UVB phototherapy and tetrahydrocurcuminoid (derived from curcuminoid) was found to be more effective than UVB phototherapy alone [40]. Oxidative stress has been suggested as the initial pathogenetic event in melanocyte degeneration in vitiligo. Curcumin increase MAPK/ERK phosphorylation, to inhibit apoptosis and pretreatment with these natural antioxidants inhibit caspase activation, increase total antioxidant capacity, repress intracellular reactive oxygen species generation and lipid peroxidation, and improve mitochondrial activity, suggesting that antioxidants such as curcumin might represent an alternative approach to protect against vitiligo progression [41]. However, Schallreuter and Rokos cautioned that in the presence of low semiquinone radicals, curcumin acts as a free radical trap and in the presence of high concentrations, the reactive oxygen species generation is over-riding, suggesting that curcumin may contribute to the oxidative stress in acute vitiligo and prevent repigmentation [35].

3. Skin Regeneration

3.1. Wound Healing

Skin regeneration and wound healing is a complex process, which involves many cell types, such as epidermal, fibroblastic, and endothelial cell, and various process such as proliferation, cell migration, matrix synthesis, and contraction. In embryos, wound healing involves repair processes that

essentially result in perfect regeneration of damaged tissue [42]. The contribution of each cell types and how these signals control wound cell activities during the healing in the skin is not well defined. Inflammation and oxidative stress during wound healing generally inhibits tissue remodeling. In healthy skin, superficial wounds are expected to heal without incident whereas wounds in chronically damaged or atrophic skin heal more slowly and often lead to nonhealing ulcers with deadly consequences [43]. Wound healing is a complex and dynamic process of restoring cellular structures and tissue layers. In general, wound healing progresses in an arranged and conventional fashion such as inflammation (reactive), proliferation (regenerative), and maturation (remodeling). There are several factors that contribute to impaired wound healing including diabetes and oxidative stress. Various investigators showed that curcumin treatment reduces wound-healing time, improved collagen deposition, and increased fibroblast and vascular density in wounds thereby enhancing impaired wound healing. It has also been shown that curcumin acts as a proangiogenic agent in wound healing by inducing TGF-β, in both normal and impaired healing wounds [2,44,45]. Curcumin that has anti-inflammatory effect by inhibiting NF-κB, acts as a supportive matrix for the regenerative tissue when incorporated in collagen matrix thereby supporting dermal wound healing [46]. It has also been shown by Jagetia and Rajanikant (47) that pretreatment with curcumin may accelerate the healing of irradiated wound by enhancing the synthesis of collagen, hexosamine, DNA, and nitrate [47]. Sidhu et al. observed faster wound closure, re-epithelialization of the epidermis and increased migration of various cells including myofibroblasts, fibroblasts, and macrophages in the wound bed of curcumin-treated animals [44]. They also observed greater collagen deposition, increase in TGF-β1, and fibronectin in curcumin-treated wounds [45].

It has also been shown that pretreatment with curcumin reduces the unburned skin interspaces that develop to full necrosis [48], and has a favorable effect on the irradiated wound healing thus presenting a substantial therapeutic strategy for both radiation-induced skin injuries [49] and laser-induced skin wounds [50]. In a metabolic impaired wound healing model, curcumin improves noevascularization and faster wound healing and was effective both orally and topically [51]. Curcumin also regulated TGF-β signaling and inducible nitric oxide synthase levels to significantly accelerate healing of wounds with or without dexamethasone treatment [45]. Angiogenesis, the formation of new blood vessels play a pivotal role during wound healing and curcumin acts as a proangiogenic agent during the critical process of wound repair by regulating TGF-β [45]. Based on these findings, it has been hypothesized that TGF-β1 might play an important role in the enhancement of wound healing by curcumin and indicate the beneficial effects of curcumin.

3.2. Antiaging

Aging caused by the genes we inherit is intrinsic (internal), due to passage of time is chronological and due to environmental factors such as exposure to the sun's rays and dryness is extrinsic (external), which leads to premature aging. Aging of the skin involves degradation of extracellular matrix in both the epidermal and dermal layers, which modifies the physical properties of skin and leaves visible signs on the surface [52].

Various synthetic skin care cosmetics are available to treat premature aging with common adverse reactions such as allergic and irritant contact dermatitis, phototoxic, and photoallergic reactions. Various phytomolecules, such as curcumin, epicatechin, ginsenoside, gallic acid, and hydroxyl-(chavicol, cinnamic, and benzoic acids), have shown to protect skin from wrinkles, leading to glowing, and healthy younger skin [52]. It has also been shown that curcumin responds to cellular stress in normal human skin fibroblasts through phosphatidylinositol 3-kinase/Akt pathway and redox signaling, which can be useful for antiaging intervention [53]. The study by Bala et al. showed that the administration of curcumin can significantly decrease the normal aging-related parameters such as lipid peroxidation, lipofuscin concentration, and intraneuronal lipofuscin accumulation and significant increase in the enzymes superoxide dismutase, glutathione peroxidase, and Na(+), K(+), -adenosine triphosphatase (Na(+), K(+), -ATPase, indicating the antioxidative, antilipofusinogenesic effects of curcumin [54]. Curcumin-supplemented diet in drosophila resulted in lifespan extension and provided new insights for antiaging mechanism of curcumin [55].

3.3. Scar Formation

Scar, the formation of fibrous tissue after wound healing of large skin injury in adults may result in abnormal skin function as well as psychological trauma. Curcumin rapidly induces the synthesis of heme-oxygenease-1, a well-known marker of intracellular stress in human skin fibroblasts [56,57]. The direct induction of heme-oxygenease-1 and coinduction of heat shock protein shows that curcumin has an effect on wound healing, cellular aging, and other functional characteristics, such as differentiation, angiogenesis, as well as scar formation [58]. Scharstuhl et al. showed that high dose of curcumin can provide a novel way to modulate pathological scar formation through the induction of fibroblast apoptosis. Curcumin act as a putative apoptosis inducing factor by inducing heme-oxygenase activity and its effector molecules [59]. Therefore, treatment with curcumin provides a novel way to modulate pathological scar formation through the induction of fibroblast apoptosis [59]. Furthermore, curcumin act similar to cathepsin-inducing drugs by increasing the cell proliferation, migration, and expression of surrogate markers of apoptosis, which may be beneficial in the treatment of fibrosis [60].

4. Anticancer Effects of Curcumin

Skin cancer is the most common cancer in human beings and melanoma is most deadly form of skin cancer, which is notoriously aggressive and chemoresistant to present therapies [61]. Cancer chemoprevention is defined as use of dietary or

pharmacologic agents to inhibit or reverse the development of cancer. Curcumin is known for its chemopreventive and anticarcinogenic activity. It has been shown to induce autophagy along with apoptosis in the treatment of melanoma, which provides a nontoxic option for combinatorial chemotherapy with significant potential [61].

NF-κB has been reported to play a central role in cell survival and growth in many types of cancer including melanoma. Curcumin has been shown to inhibit NF-κB activity in several cell types and selectively inhibit the growth of melanoma cells, but not normal melanocytes [62]. Curcumin induced apoptosis and inhibit NF-kappa B-driven reporter activity with decreased levels of phospho-I κB α, and also decreased expression of NF-κB-target genes like *COX-2* and *cyclin D1* in melanoma cells. Curcumin also inhibited skin squamous cell carcinoma growth and blocks tumor progression by inhibiting mTOR signaling. Dibenzoylmethane, a β-diketone structural analogue of curcumin, has also been reported to exhibit antitumorigenic and chemopreventive activities [63]. It has also been shown that curcumin inhibit 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced tumor promotion and TPA-responsive markers in mouse skin [64]. The protein kinase C (PKC), the major cellular receptor of TPA, mediates TPA-induced biological responses in mouse skin and curcumin modulates transmembrane signal transduction via PKC to affect TPA-induced biochemical and molecular alterations in mouse skin.

Photocarcinogenesis is caused by DNA damage to the skin from solar radiation in the ultraviolet range and resulting in the development of both melanoma and nonmelanoma skin cancers. Curcumin has been shown to protect against the deleterious effects of injury by attenuating oxidative stress and suppressing inflammation [64]. Curcumin block multiple targets of these pathways and can be used in the chemoprevention of photoaging skin and photocarcinogenesis. Curcumin not only activates caspase-3 and caspase-8 in human melanoma cell lines, it also induces activation of a death receptor pathway, by inducing Fas receptor [64].

5. Development of Transdermal Delivery Systems to Enhance Bioavailability of Curcumin

Curcumin is one of the most health beneficial components of turmeric. One of the biggest challenges to use curcumin as a therapeutic and nutritional supplement effectively is the poor solubility, bioavailability, and photostability of curcumin in its raw form. Studies to date have shown the reduced bioavailability of curcumin within the body is due to high intrinsic activity, poor absorption, rapid metabolism, inactivity of metabolic products, and/or rapid elimination and clearance from the body [1]. To overcome these limitations, efficacious formulations of curcumin, including nanocrystal solid dispersion, amorphous solid dispersion, and nanoemulsion, are being developed [65]. Some adjuvants that may block metabolic pathways of curcumin are also being used to improve the bioavailability of curcumin. Other promising formulations such as liposomes, micelles, nanoparticles, and phospholipid complexes, which provide longer circulation, better permeability, and resistance to metabolic processes are also being used [1].

In vitro skin penetration study showed that curcumin- soybean phospholipids-loaded liposomes can significantly endorse drug permeation and deposition and also inhibited the growth of melanoma cells to a greater extent. These results suggest that curcumin-soybean phospholipids-loaded liposomes may act as a transdermal carrier for curcumin in cancer treatment [66]. Earlier, Wang et al. developed doxorubicin (DOX)-loaded long circulating liposomes combined with curcumin (CUR) (DOX-CUR-LCLs), as a novel formulation for cancer treatment. Cytotoxicity evaluation showed that DOX-CUR-LCLs had a significantly higher antitumor activity than other DOX preparations. These observations suggest that this novel DOX-CUR-LCLs, combination of DOX and CUR administered in long-circulating liposomes, could possibly improve antitumor activity [67].

Recently, a new magnetic-based core-shell particles (MBCSPs) were also developed to target skin cancer cells to deliver chemotherapeutic drugs in a controlled way. These particles are made up of a thermo-responsive shell of poly (*N*-isopropylacrylamide-acrylamide-allylamine) and a core of poly(lactic-*co*-glycolic acid) (PLGA) embedded with magnetite nanoparticles. These shell particles have unique multifunctional and controlled drug delivery characteristics with an ability to provide dual drug release mechanisms (a sustained release of drugs through degradation of PLGA core and a controlled release in response to changes in temperature via thermoresponsive polymer shell), and dual targeting mechanisms (magnetic localization and receptor-mediated targeting) [68]. *In vitro* studies demonstrated a sustained release of curcumin from the core and a temperature-dependent release of doxorubicin from the shell of MBCSPs were observed with no cytotoxicity to normal fibroblasts [68]. MBCSPs has a great potential as a platform technology to target, treat and monitor melanoma for targeted drug delivery and to reduce the side effects of chemotherapeutic reagents [68].

As an alternative to traditional gels for the topical applications of hydrophobic drugs, Koop et al. demonstrated that the xanthan-galactomannan (X:G) hydrogels system with addition of curcumin in microemulsion, exhibited a significantly higher elastic response. *In vitro* skin permeation tests showed a more pronounced lag time and more efficient permeation with their novel delivery system [69]. Similarly, curcumin loaded chitin nanogels (CCNGs) were developed, using biocompatible and biodegradable chitin. Both chitin and curcumin are insoluble in water but CCNGs developed by Mangalathillam et al. form a very good and stable dispersion in water and their study suggested that the formulated CCNGs have specific advantage for the treatment of melanoma, the most common and serious type of skin cancer, by effective transdermal penetration [70].

Recently, Ratanajiajaroen and Ohshima developed spherical curcumin-incorporated chitin porous beads in which Tween 20 was used to enhance the solubility of curcumin in the chitin beads during the incorporation step. The amount of Tween 20 also played an important role in the release characteristic of curcumin from the chitin matrix. The internal pores and the outer nonporous shell structure of the chitin beads determined the curcumin-releasing behavior. The internal porous structure could dramatically increase the uptake of the releasing medium, while the nonporous outer skin layer dominated the slow releasing behavior of curcumin. They successfully postulated the entrapment of curcumin into the cores of Tween 20 micelles encapsulated in the chitin shell as a promising candidate for drug delivery devices [71]. So far, loading of nanoscaled or microscaled carriers has enabled only an uptake up to 30% of curcumin. To enhance the delivery of curcumin, Suwannateep and his group [72] exploited the application of ethylcellulose blended with methylcellulose to improve the penetration of curcumin in all formulations. The study shows that high loaded encapsulated curcumin systems, prepared from a simple and highly efficient encapsulation system may be used to transport curcumin effectively in the skin [72].

Gupta and Dixit [73] used the vesicular system for delivery of curcumin to achieve enhanced topical bioavailability and to attain significant antioxidant and antiaging effect. The combination of curcumin with phosphatidyl choline was prepared and converted into phyto-vesicles. Liposomes and niosomes of curcumin were also prepared and all these vesicular formulations were incorporated into carbopol gel to make topical application feasible. The phyto-vesicles were found to be most effective compared to all other formulations and plain curcumin in providing enhanced antioxidant and antiaging effect. This increase may be due to the amphiphilic nature of the complex, which greatly enhances the water and lipid miscibility of the curcumin. This indicates the superiority of phytovesicles prepared from curcumin-phosphatidyl choline complex in providing enhanced antiaging, antioxidant, and antiwrinkle effect [73].

Rungphanichkul et al. showed that curcuminoids can be successfully formulated as niosomes by series of Span nonionic surfactants to enhance the skin permeation of curcuminoids and improve its properties for transdermal delivery [74]. Liu and Chang developed aneucalyptol microemulsion system as a promising tool for the percutaneous delivery of curcumin [75]. Microemulsions have been extensively studied for the applications in transdermal drug delivery. The solubility of curcumin in various oils, surfactants, and cosurfactants were studied to find the optimal components for a transdermal delivery vehicle and microemulsions were successfully developed for transdermal curcumin delivery after screening various components and adjusting the oil/water ratios [75]. Microemulsions loaded with curcumin were successfully optimized for transdermal delivery after screening various terpenes, cosurfactants, and limonene/water ratios, and it was found out that the limonene microemulsion system is a promising tool for the percutaneous delivery of curcumin [76]. Further, Chaudhary et al. developed and optimized a transdermal gel formulation for diclofenacdiethylamine and curcumin. They successfully showed that permeation rate of diclofenacdiethylamine decreased with polymer concentration, whereas the permeation rate of curcumin increased proportionally with polymer concentration [77]. Patel et al. developed and studied the topical gel delivery of curcumin for its anti-inflammatory effects and showed that Carbopol 934P gel showed better inhibition of inflammation [78]. There is very little knowledge about the localization of the drugs within the skin and the stratum corneum. Teichmann et al. showed that lipophilic dye curcumin incorporated in an oil-in-water microemulsion and as an amphiphilic cream was applied onto the skin and a deeper part of the stratum corneum was accessible and significantly smaller amounts of curcumin was found on the skin surface [79]. Furthermore, curcumin was detected in hair follicles, so it is obvious that the microemulsion led to a penetration into the complete follicular infundibula [79]. An *in vivo* animal study by Dai et al. demonstrated that sponge has better effect than cotton gauze, and adding curcumin into the sponge enhanced the therapeutic healing effect [80]. A biodegradable sponge, composed of chitosan and sodium alginate, was successfully obtained and swelling ability, *in vitro* drug release and degradation behaviors, and an *in vivo* animal test were used to confirm the applicability of this sponge as a wound dressing material. The release of curcumin from the sponges could be controlled by the cross linking degree [80]. The study by Thangapazham et al. [81] showed the enhancement of targeted delivery of an anticancer agent, curcumin, for cancer treatment by incorporating this agent into the liposomes (nanodelivery vehicles primarily composed of phospholipids). They prepared curcumin-loaded liposomes of various lipid compositions by sonication and considered the use of liposomes as a delivery model for curcumin [81]. The cell proliferation assays provide strong evidence for liposomes as effective nanodelivery vehicles that increase the bioavailability of curcumin [81].

Swaroop et al. demonstrated the formation of inclusion complex of curcumin with β-cyclodextrin and the complex formation changes curcumin into a water-soluble form and showed increase superoxide scavenging ability of curcumin [82]. Recently, Ghosh et al. showed that incorporation of curcumin in nanoscale disk-shaped phospholipid bilayers can overcome the poor water solubility of curcumin bioactive molecule and may have *in vivo* therapeutic applications [83]. Further, the solubility of curcumin can also be enhanced by using the solubilizing properties of rubusoside (RUB). It has been shown by Zhang et al. that RUB-solubilized curcumin was stable in physiological conditions and did not precipitate when diluted or degrade when spray-dried to a completely reconstitutable powder [84]. Further, it has also been established by cell viability assays, which demonstrate the better efficacy of RUB-solubilized curcumin against human colon, breast, and pancreatic cancer cell lines. The development of this new solubilized, stable, and biologically active curcumin formulation can provide improved curcumin bioavailability [84].

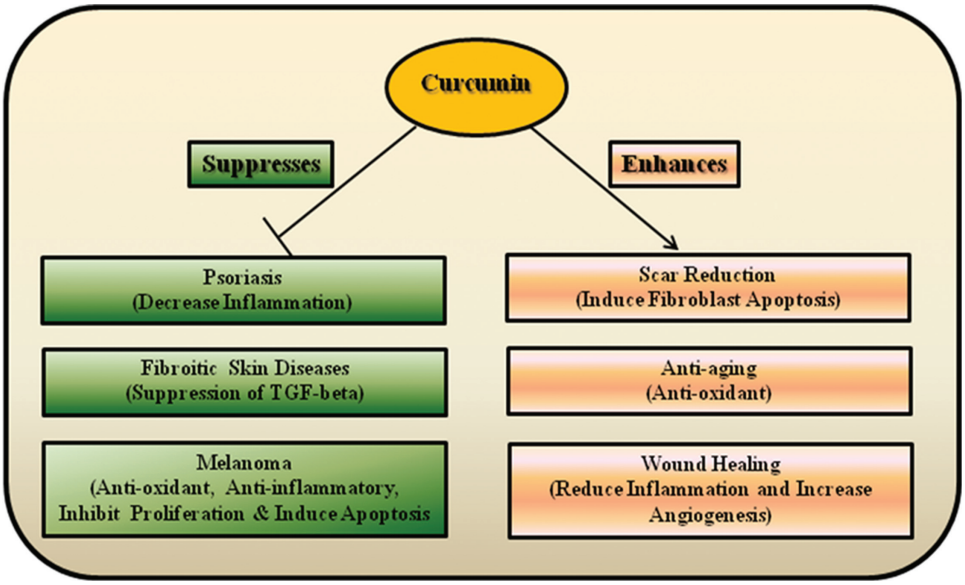

FIG 1 *Effect of curcumin in skin with proposed novel mechanism(s).*

6. Clinical Trials in Skin

Curcumin has been demonstrated to inhibit carcinogenesis of murine skin, stomach, intestine, and liver *in vitro* [85]. However, the toxicology, pharmacokinetics and biologically effective dose of curcumin in humans have not been fully evaluated. Cheng et al. performed a clinical trial for curcumin, as a chemopreventive agent, in patients with high-risk or premalignant lesions like urinary bladder cancer, arsenic Bowen's disease of the skin, uterine cervical intraepithelial neoplasm, oral leucoplakia, and intestinal metaplasia of the stomach demonstrating nontoxic nature of curcumin even at higher doses [86]. Pharmacologically active concentration of curcumin can be achieved in colorectal tissue in patients taking curcumin orally and might also be achievable in tissues such as skin and oral mucosa when applied topically or locally [87]. The authors also reviewed the effect of curcumin in patients with rheumatoid arthritis, inflammatory eye diseases, inflammatory bowel disease, chronic pancreatitis, psoriasis, hyperlipidemia, and cancers. The results of this study were not conclusive and did not support the efficacy of curcumin in these diseases. It been suggested that well-designed clinical trials, supported by better formulations of curcumin or novel routes of administration, be conducted in the near future [87].

Skin gets most heavily damaged upon exposure to sulfur mustard (SM) and causes pruritus, the most common chronic skin complication of SM. Currently, there are very limited therapies available for the management of SM-induced pruritus. The clinical trial by Panahi et al. on 96 male Iranian veterans showed the efficacy of curcumin in the alleviation of SM-induced chronic pruritic symptoms [88]. Serum concentrations of superoxide dismutase, glutathione peroxidase, and catalase were significantly reduced in curcumin group, whereas no significant change was observed in the placebo group. Curcumin supplementation was also found to be associated with significant reductions in measures of pruritus severity including the pruritus score. None of these measures were significantly changed in the placebo group which leads to the conclusion that curcumin may be regarded as safe and inexpensive treatment for the management of SM-induced chronic pruritus [88].

7. Conclusions

The most commonly studied pathway through which curcumin exerts its beneficial effect is NF-κB. Curcumin inhibits NF-κB, subsequently reducing inflammation and thereby providing benefits for various skin diseases. Recent studies as reviewed here are unraveling previously unidentified pathways, unique molecular targets and novel mechanisms through which curcumin may perform as a skin protectant (Fig. 1). We believe that continuous research will increase the disease portfolio for which curcumin may be beneficial and hope that future clinical trials will lead to the development of curcumin as a chemopreventive agent.

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